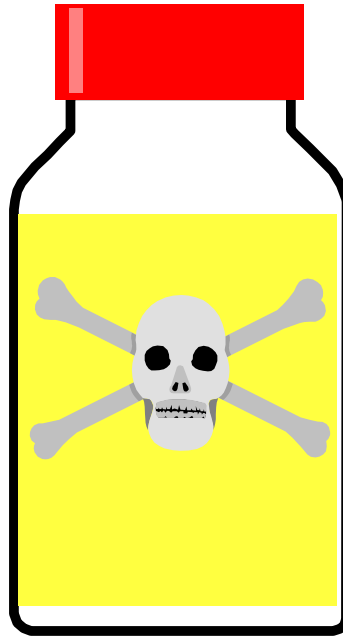


بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

Dr Reza Najafipour  
M.D. Ph.D. M.P.H.

# Mutations



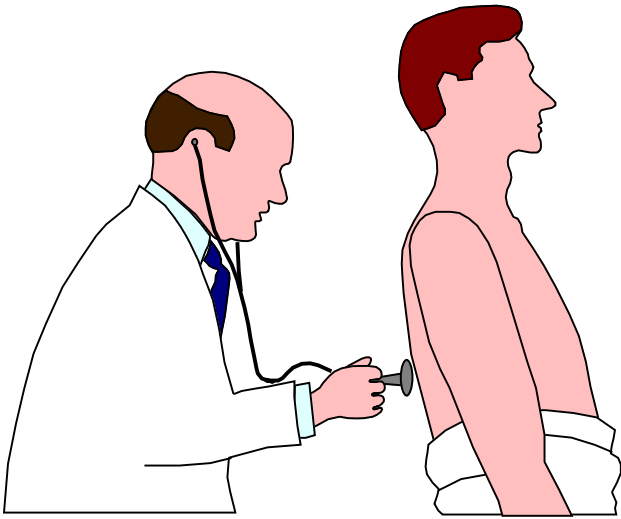
# Mutation: damage to genetic material

A mutation to genetic material is usually not beneficial. Mutagens are things that cause mutations, they include:

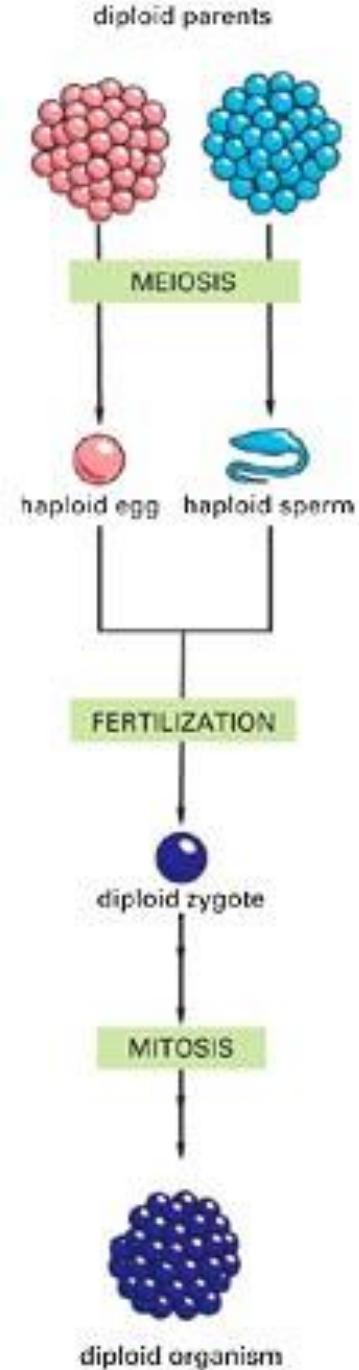
1. High Temperatures
2. Toxic Chemicals (pesticides, etc)
3. Radiation (nuclear and solar)

Many common place items are capable of causing mutations: microwave, fruit from the store, radar, cellular phones....

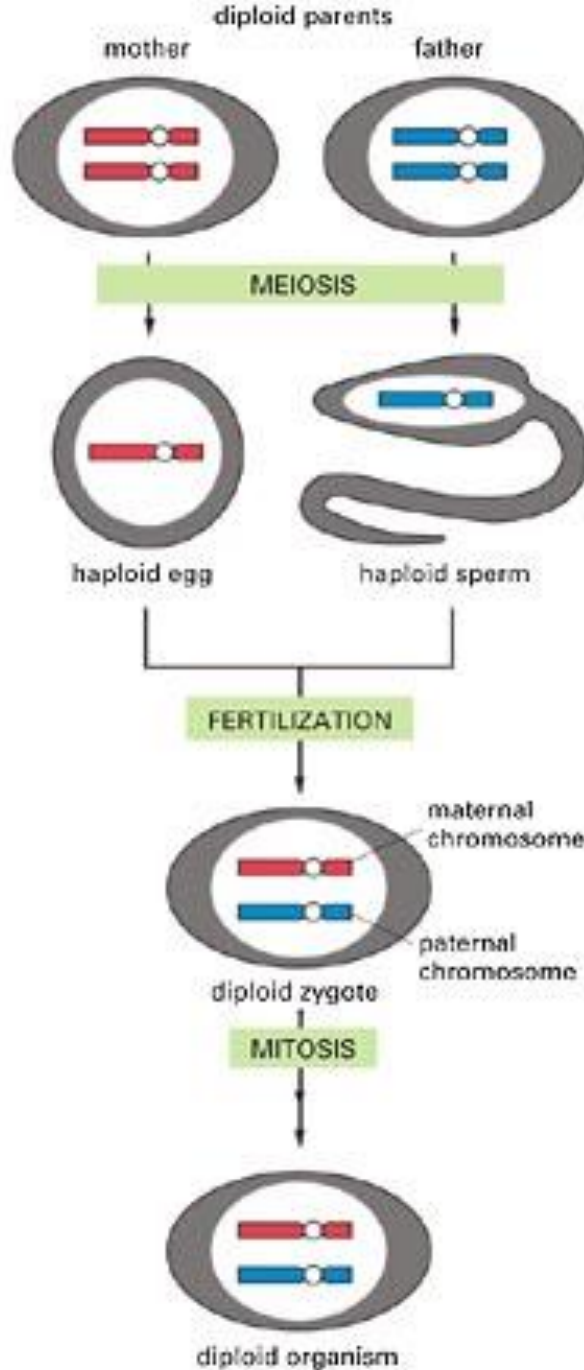
# Somatic vs Germ Mutations



Some people may have mutations in their skin cells or hair. Such mutations are termed Somatic. Germ mutations occur only in the sex cells. These mutations are more threatening because they can be passed to offspring (forever).



(A)

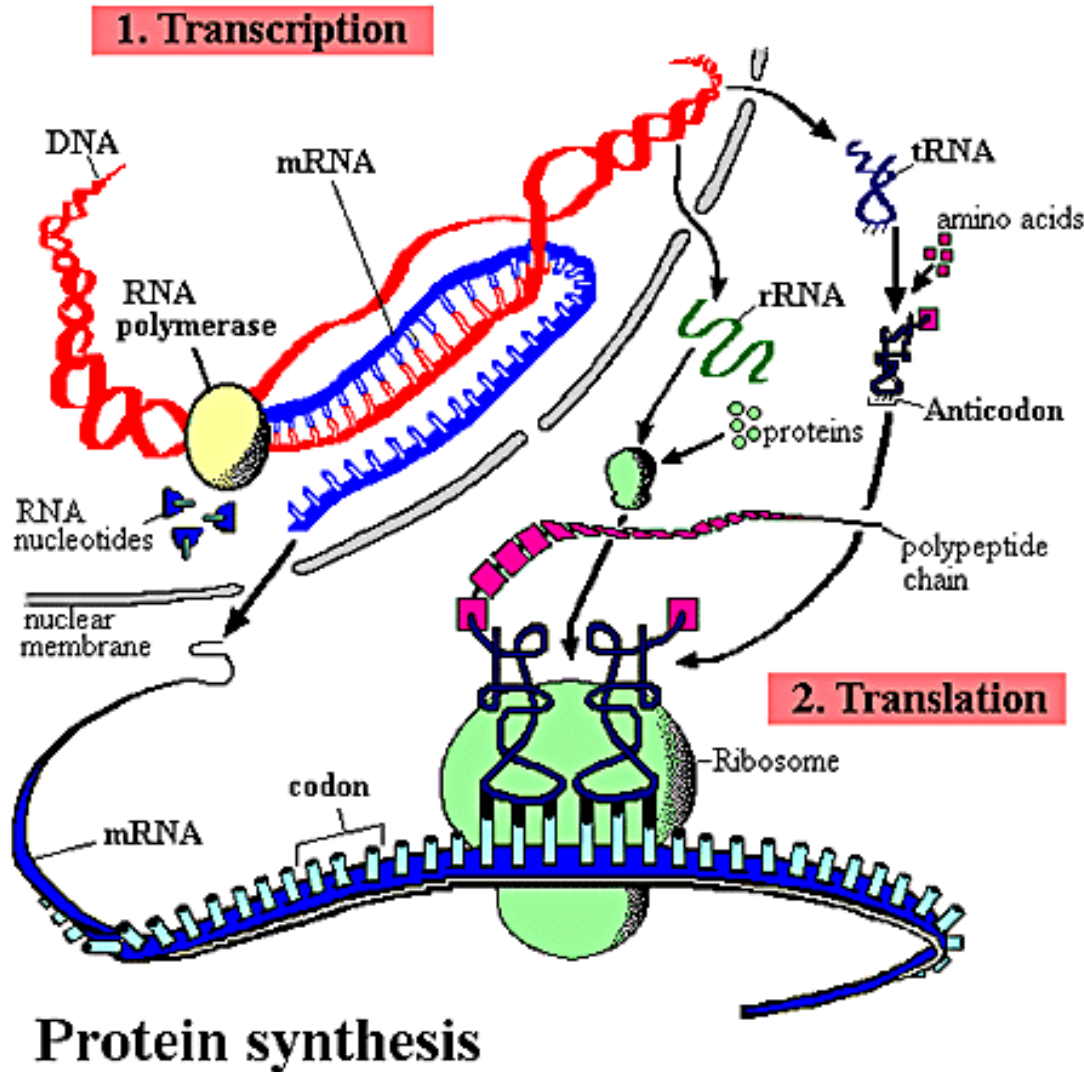


(B)

Meiosis is a prime time for mutations to occur.

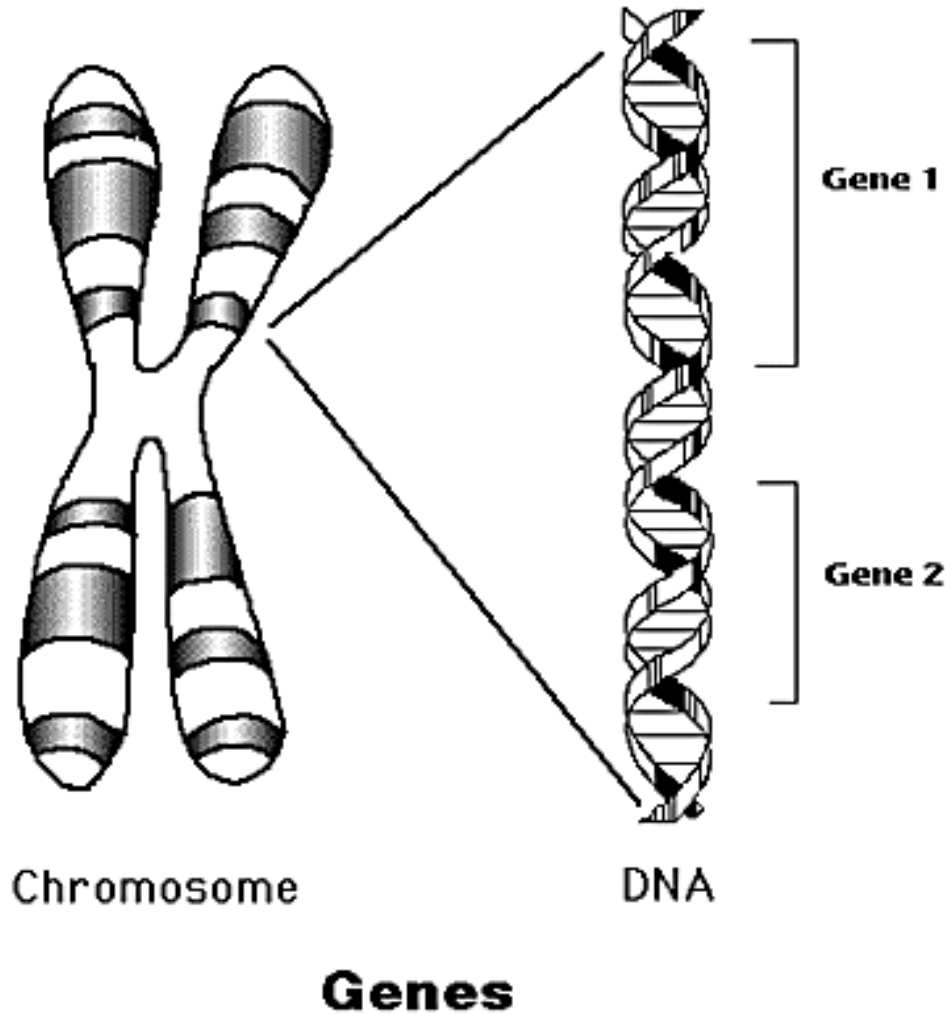
The germ mutations that occur during meiosis could be passed on during a fertilization

# Mutations effect protein synthesis



Transcription:  
Mutated DNA  
will produce  
faulty mRNA  
leading to the  
production of a  
bad protein.

# Types of mutations



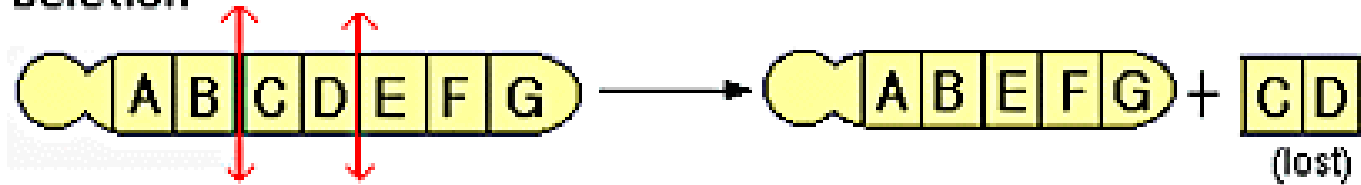
**Chromosomal:**  
affecting whole  
or a part of a  
chromosome

**Gene:** changes  
to the bases in  
the DNA of one  
gene

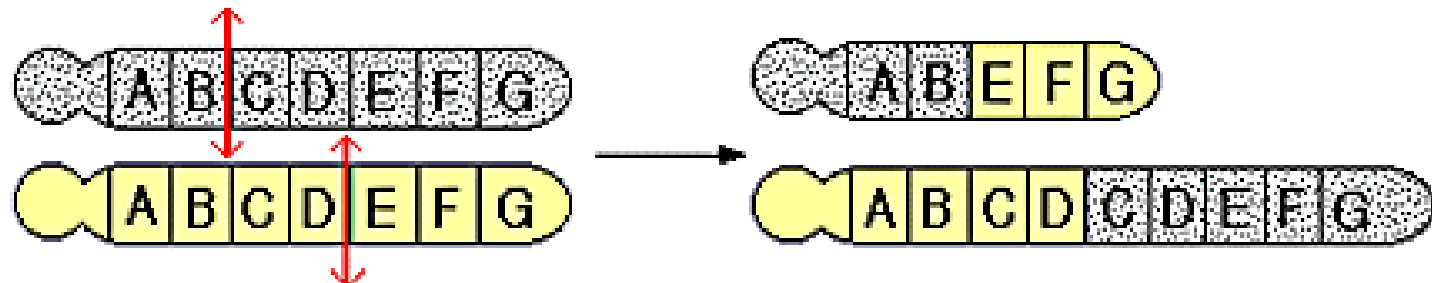
## Point mutation



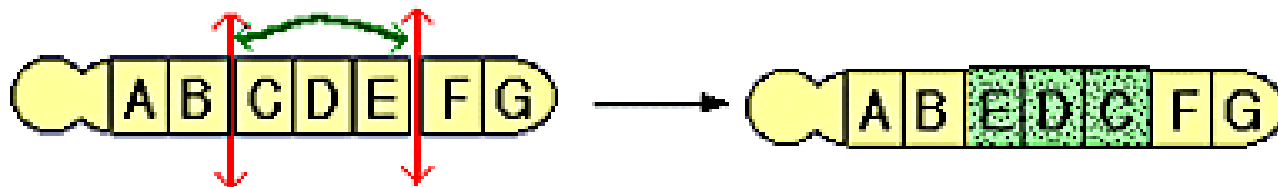
## Deletion



## Translocation



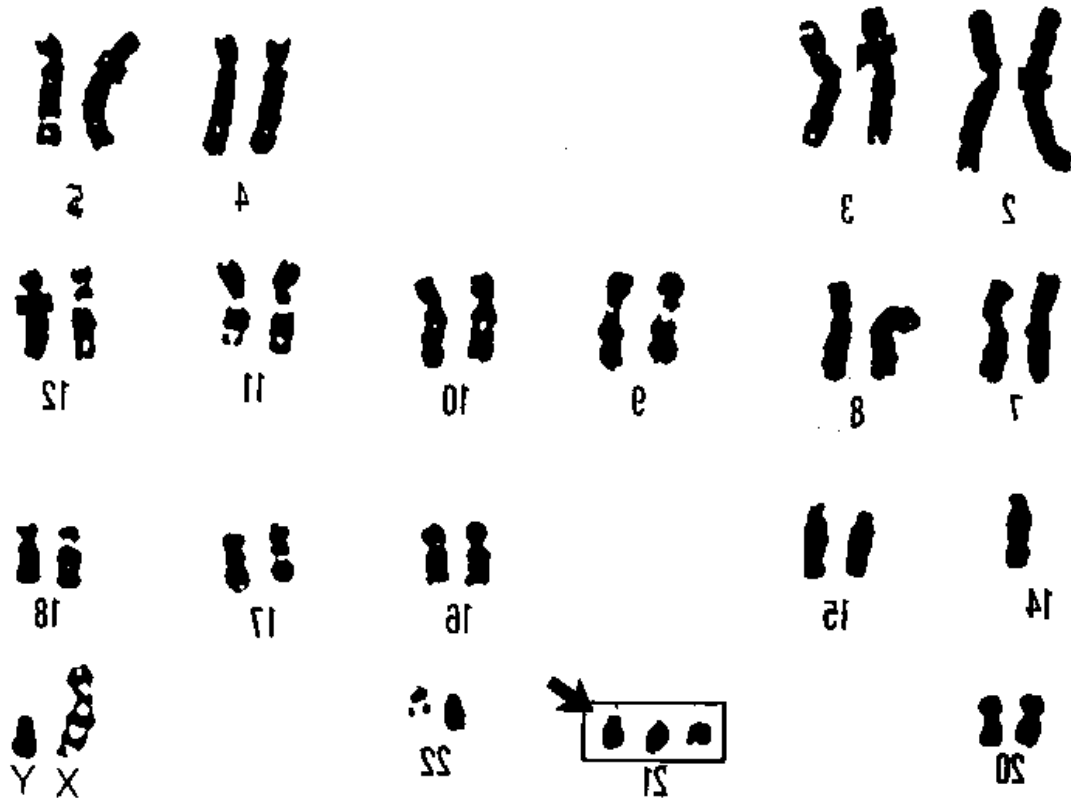
## Inversion



# Mutations of Chromosomes

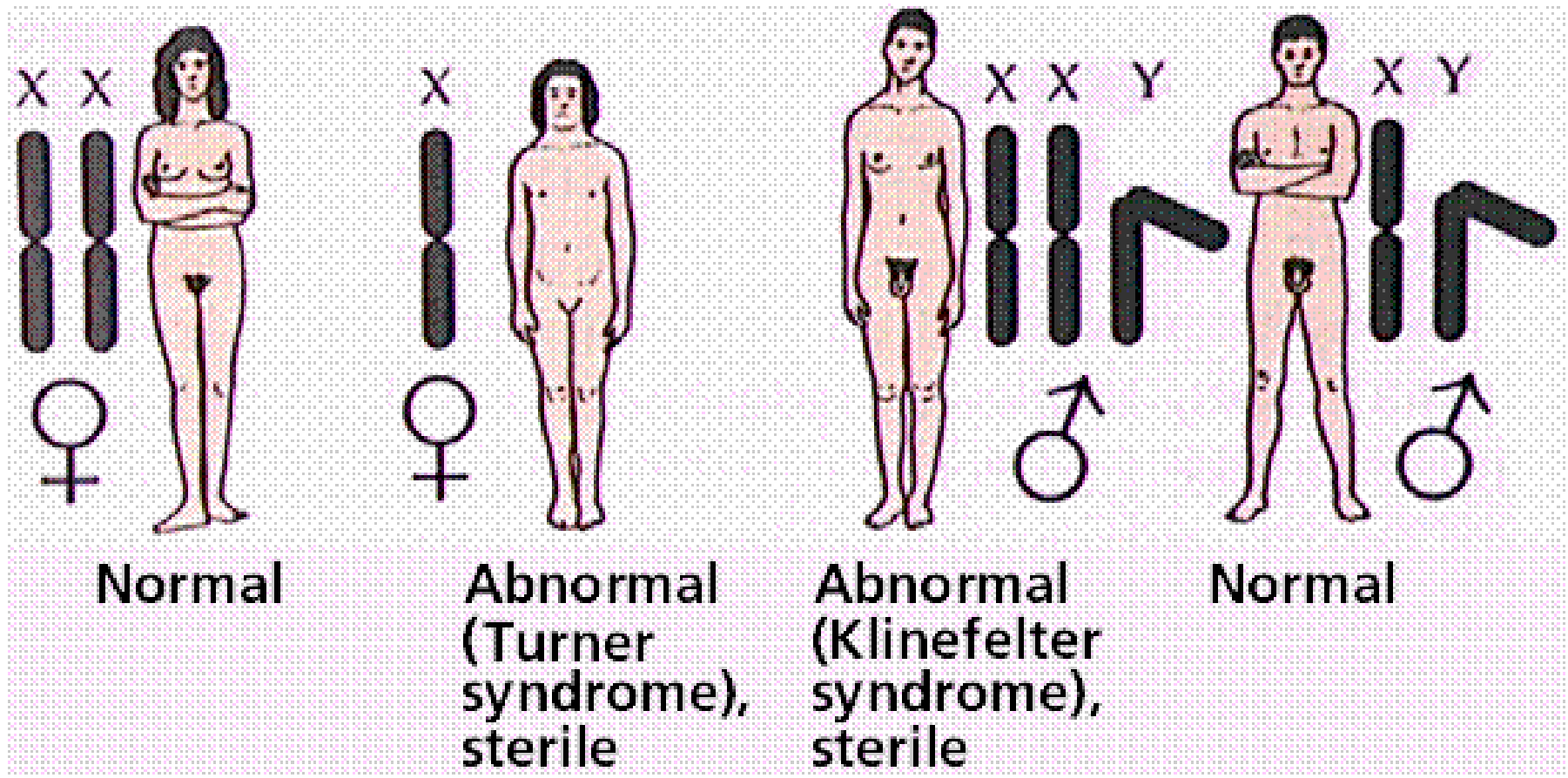


# Chromosome Mutations: Nondisjunction



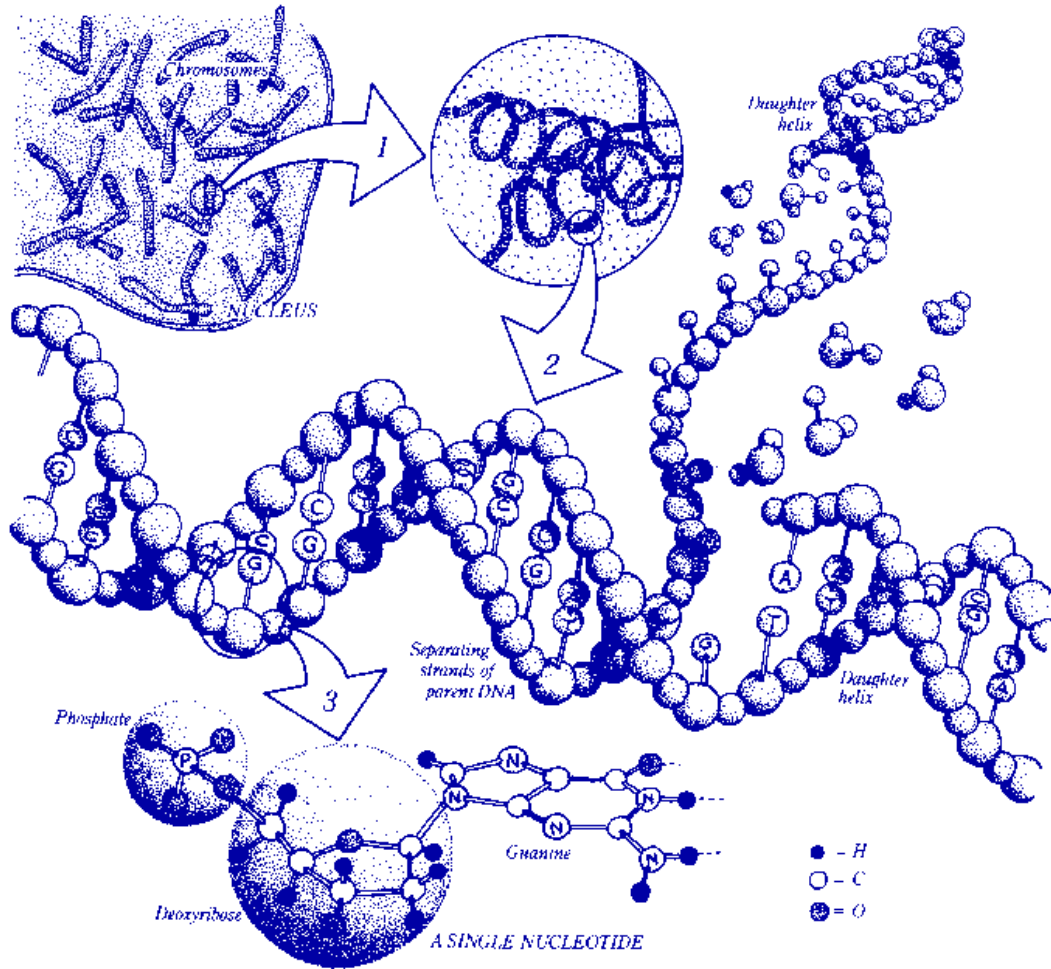
During meiosis tetrads may not segregate or in meiosis II, sister chromatids may stick together. Nondisjunction.

The above karyotype is of a person who has nondisjunction of the 21st chromosome or Down syndrome. (note the extra chromosome)



Nondisjunction of the sex chromosomes

# Gene Mutations: DNA base alterations



Point mutation  
Insertion\*  
Deletion\*  
Inversion  
\*Frame Shifts\*

Point mutation - when a base is replaced with a different base.

CGG CCC AAT to CGG C**G**C AAT

**Guanine** for Cytosine

Insertion - when a base is added

CGG CCC AAT to CGG C**G**C CAA T

**Guanine** is added

Deletion - the loss of a base

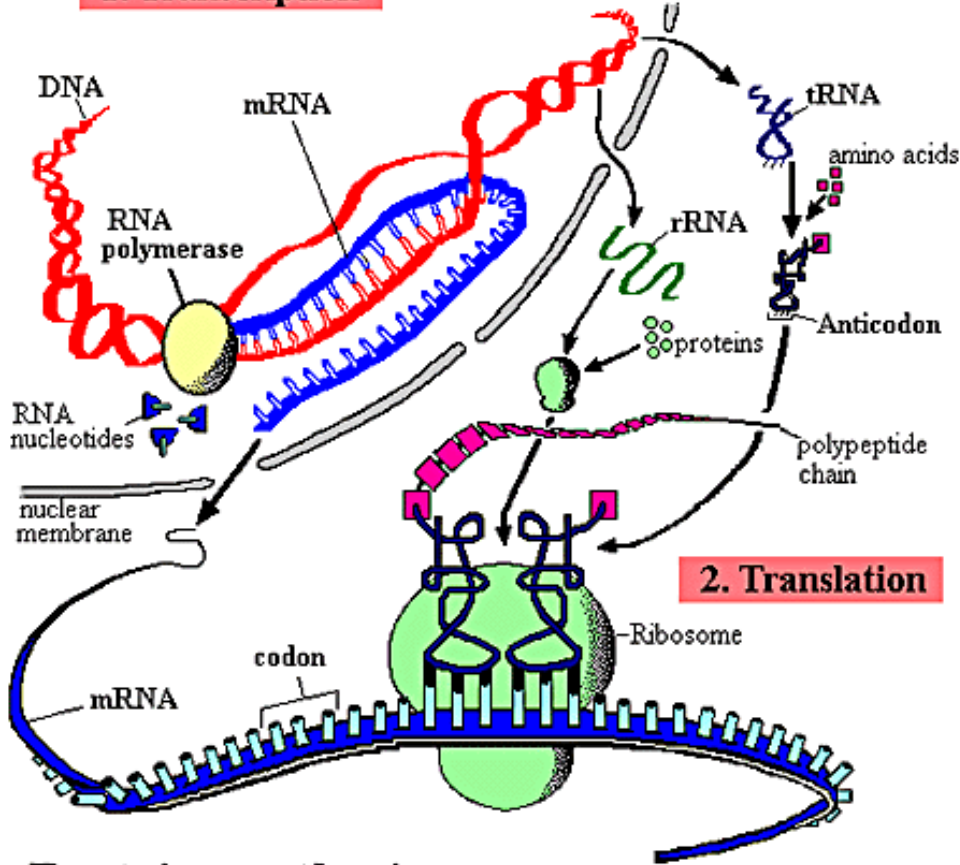
CGG CCC AAT to CGG CCA A T

loss of **Cytosine**

# Frame Shift mutations

- A frame shift mutation results from a base deletion or insertion. Each of these changes the triplets that follow the mutation.  
CGG CCC AAT to CGG C**G**C CAA T
- Frame shift mutations have greater effects than a point mutation because they involve more triplets (recall how important triplets are to protein synthesis)

## 1. Transcription



Protein synthesis

The Frame shift changes the mRNA produced.

mRNA from DNA  
as expected.....  
GGG CCC TTT AAA  
CCC GGG AAA UUU

Mutated DNA GGC GCC CTT TAA A  
CCG CGG GAA AUU U

All the triplets are changed, this in turn changes the amino acids of the protein!

Protein shape determines how a protein will function. A change in one amino acid may change the shape enough to distort the protein (as in sickle cell disease).

Thus, change in one base could potentially distort a whole protein. It is more likely that a frame shift mutation will change several triplets and distort a protein's structure.

# Types of Chromosomal Mutations

1. Variations in chromosome structure or number can arise spontaneously or be induced by chemicals or radiation. Chromosomal mutation can be detected by:
  - a. Genetic analysis (observing changes in linkage).
  - b. Microscopic examination of eukaryotic chromosomes at mitosis and meiosis (karyotype analysis).
2. Chromosomal aberrations contribute significantly to human miscarriages, stillbirths and genetic disorders.
  - a. About  $1/2$  of spontaneous abortions result from major chromosomal mutations.
  - b. Visible chromosomal mutations occur in about  $6/1,000$  live births.



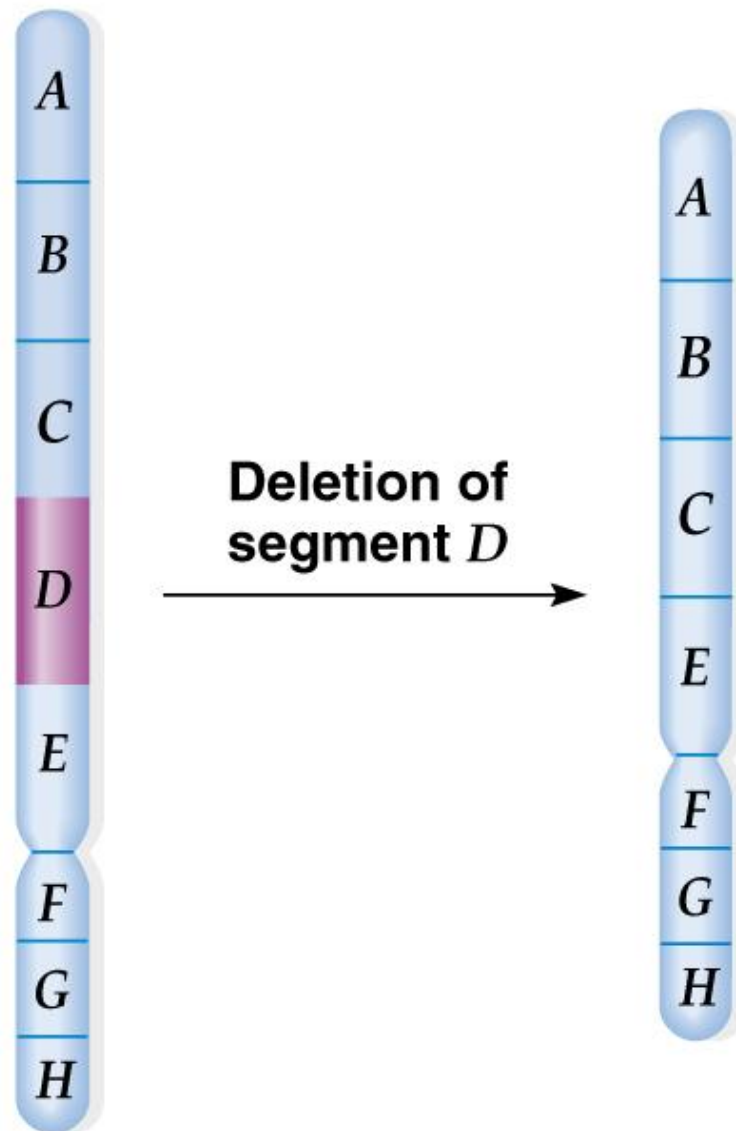
# Variations in Chromosome Structure

1. Mutations involving changes in chromosome structure occur in four common types:
  - a. Deletions.
  - b. Duplications.
  - c. Inversions (changing orientation of a DNA segment).
  - d. Translocations (moving a DNA segment).
2. All chromosome structure mutations begin with a break in the DNA, leaving ends that are not protected by telomeres, but are "sticky" and may adhere to other broken ends.

# Deletion

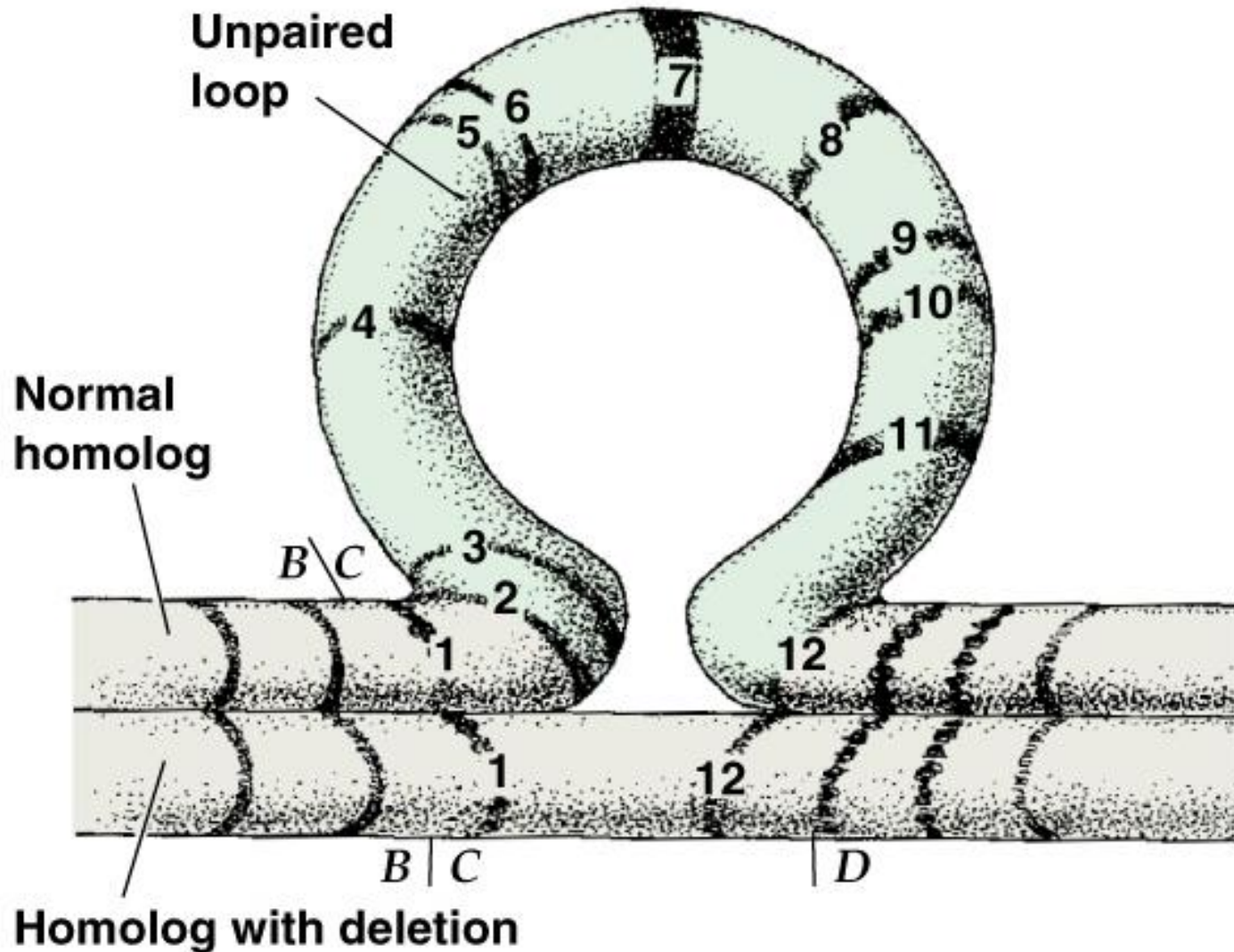
1. In a deletion, part of a chromosome is missing
  - a. Deletions start with chromosomal breaks induced by:
    - i. Heat or radiation (especially ionizing).
    - ii. Viruses.
    - iii. Chemicals.
    - iv. Transposable elements.
    - v. Errors in recombination.
  - b. Deletions do not revert, because the DNA is missing.
2. The effect of a deletion depends on what was deleted.
  - a. A deletion in one allele of a homozygous wild-type organism may give a normal phenotype, while the same deletion in the wild-type allele of a heterozygote would produce a mutant phenotype.
  - b. Deletion of the centromere results in an acentric chromosome that is lost, usually with serious or lethal consequences. (No known living human has an entire autosome deleted from the genome.)
  - c. Large deletions can be detected by unpaired loops seen in karyotype analysis.

# A deletion of a chromosome segment



# Cytological effects of meiosis of heterozygosity for a deletion

Paired polytene chromosomes



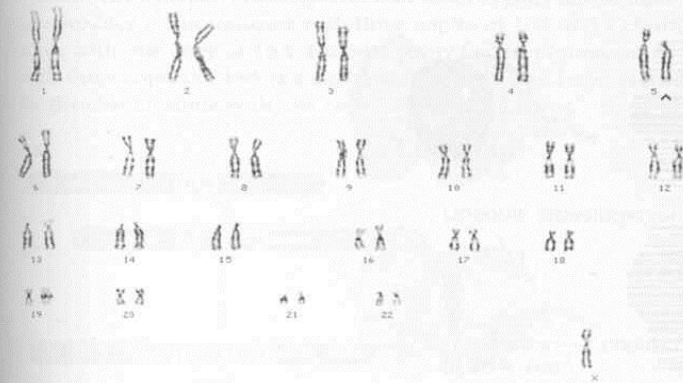
Human disorders caused by large chromosomal deletions are generally seen in heterozygotes, since homozygotes usually die. Examples include:

- a. Cri-du-chat ("cry of the cat") syndrome, resulting from deletion of part of the short arm of chromosome 5 (Figure 21.4).
- b. Prader-Willi syndrome, occurring in heterozygotes with part of the long arm of one chromosome 15 homolog deleted. The deletion results in feeding difficulties, poor male sexual development, behavioral problems and mental retardation.

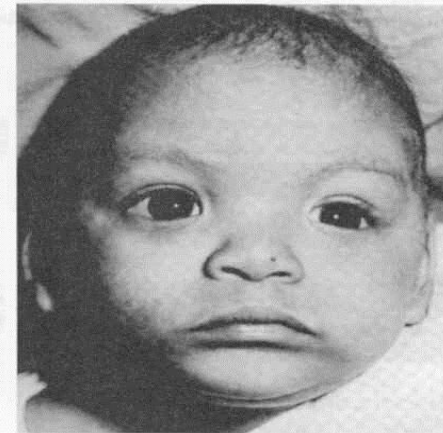
Figure 21.4

Cri-du-chat syndrome results from the deletion of part of one of the copies of human chromosome 5. (a) Karyotype of individual with cri-du-chat syndrome. (b) A child with cri-du-chat syndrome.

a)



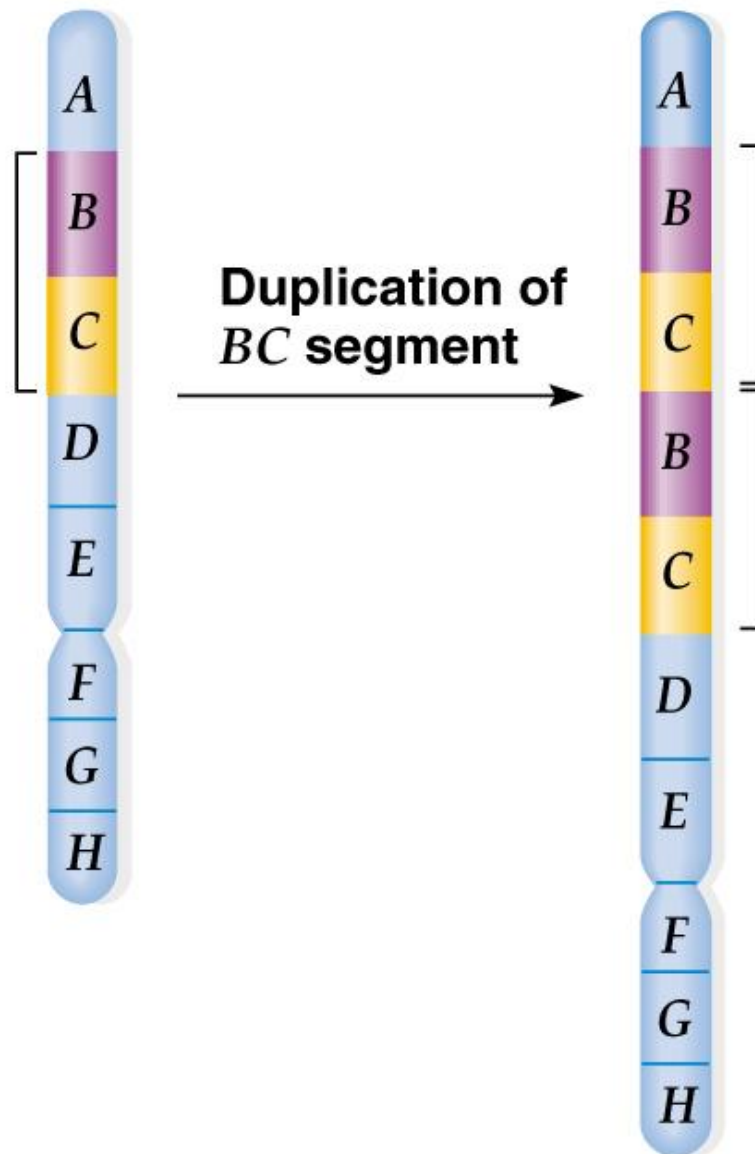
b)



# Duplication

1. Duplications result from doubling of chromosomal segments, and occur in a range of sizes and locations.
  - a. Tandem duplications are adjacent to each other.
  - b. Reverse tandem duplications result in genes arranged in the opposite order of the original.
  - c. Tandem duplication at the end of a chromosome is a terminal tandem duplication.
  - d. Heterozygous duplications result in unpaired loops, and may be detected cytologically.

# Duplication, with a chromosome segment repeated



# Forms of chromosome duplications are tandem, reverse tandem, and terminal tandem duplications

Normal chromosome



Duplications



Tandem



Reverse tandem



Terminal tandem



2. An example is the *Drosophila* eye shape allele, *Bar*, that reduces the number of eye facets, giving the eye a slit-like rather than oval appearance.

a. The *Bar* allele resembles an incompletely dominant mutation:

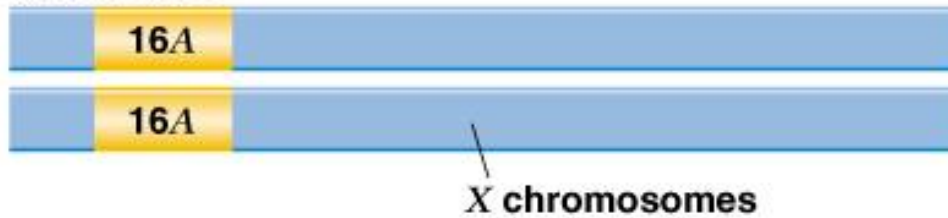
i. Females heterozygous for *Bar* have a kidney-shaped eye that is larger and more faceted than in a female homozygous for *Bar*.

ii. Males hemizygous for *Bar* have slit-like eyes like those of a *Bar/Bar* female.

b. Cytological examination of polytene chromosomes showed that the *Bar* allele results from duplication of a small segment (16A) of the X chromosome.

## Genotype

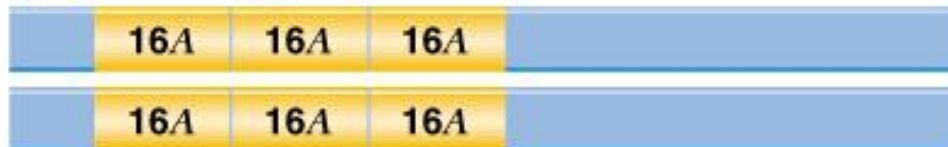
### a) Wild type



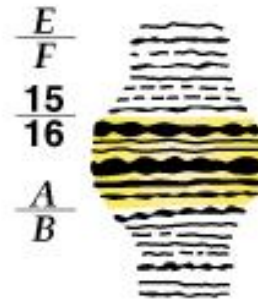
### b) *Bar* type



### c) Double*Bar* type



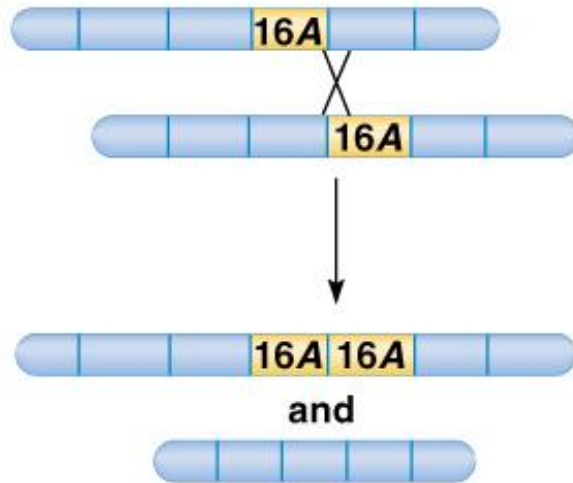
## Polytene bands



## Phenotype



a)

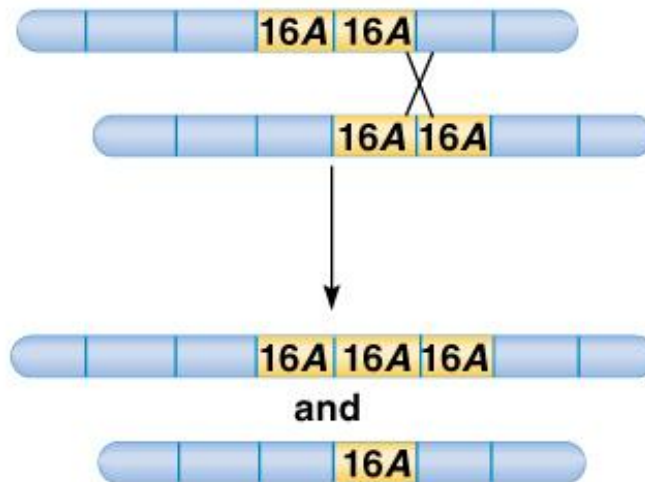


Unequal crossing-over

Duplication—2 copies  
of 16A (*Bar*)

Deletion

b)



Unequal crossing-over

Three copies of 16A  
(double-*Bar*)

One copy of 16A  
(normal)

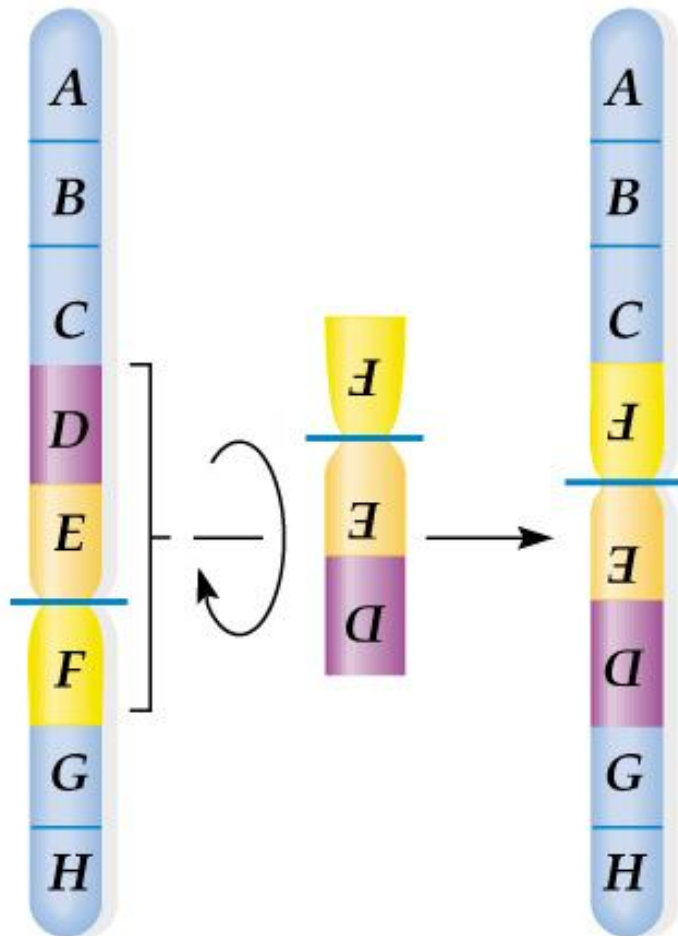
# Inversion

## Animation: Crossing-over in an Inversion Heterozygote

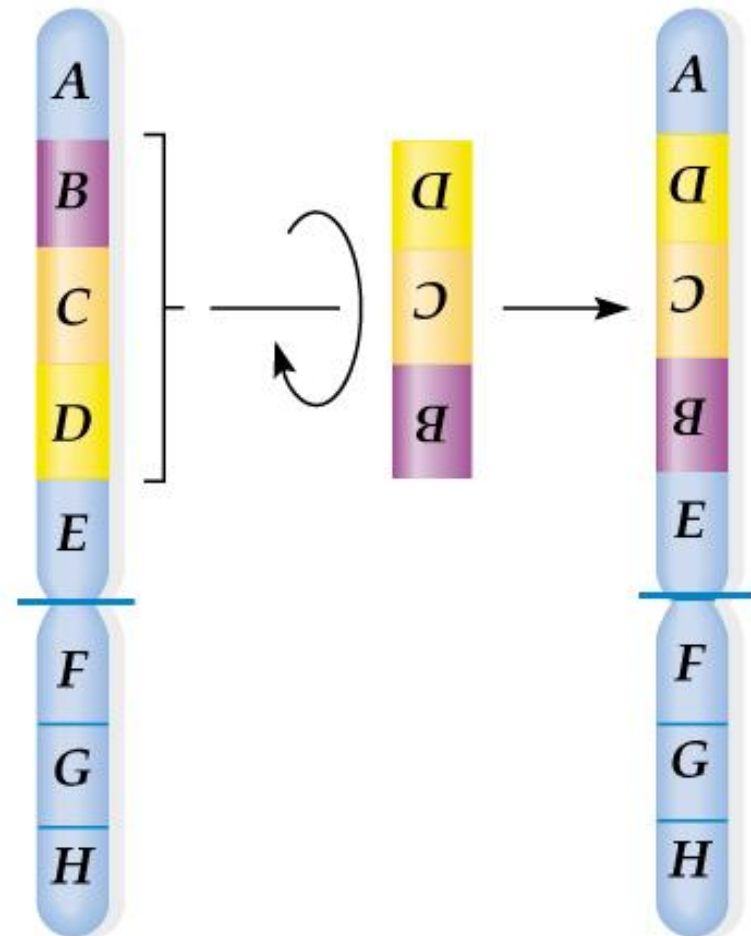
1. Inversion results when a chromosome segment excises and reintegrates oriented  $180^\circ$  from the original orientation. There are two types:
  - a. **Pericentric** inversions include the centromere.
  - b. **Paracentric** inversions do not include the centromere.
2. Inversions generally do not result in lost DNA, but phenotypes can arise if the breakpoints are in genes or regulatory regions.
3. Linked genes are *often* inverted *together*. For example:
  - a. If a normal chromosome has the gene order *ABCDEFGH*, inversion of the BCD) segment would give the gene order **ADCBEFGH**.
    - i. A fly homozygous for the inversion (**ADCBEFGH/ADCBEFGH**) will have normal crossing over and meiosis, and no problems with gene duplications or deletions.
    - ii. A heterozygote (*ABCDEFGH/ADCBEFGH*) suffers serious genetic consequences due to unequal crossover.

# Inversions

**a) Pericentric inversion  
(includes centromere)**

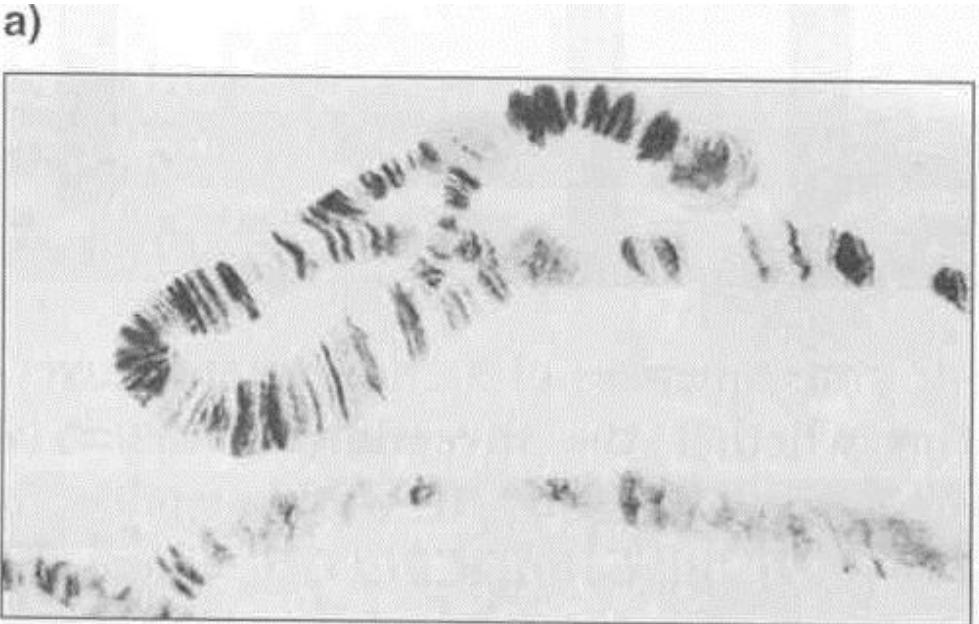


**b) Paracentric inversion  
(does not include centromere)**





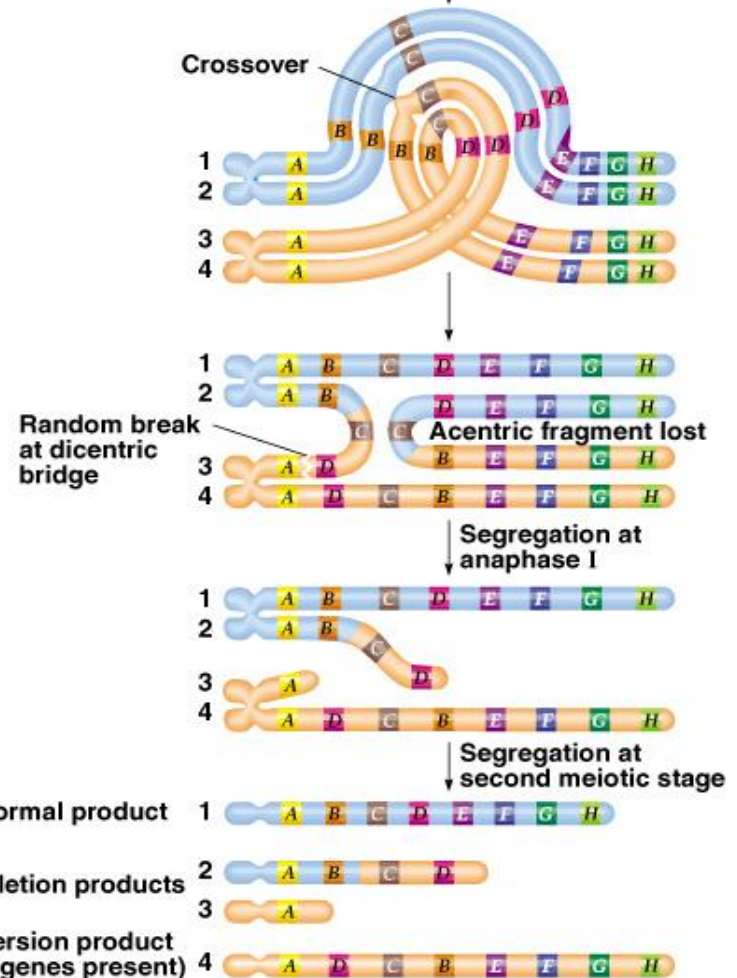
# Consequences of crossing-over in a paracentric inversion



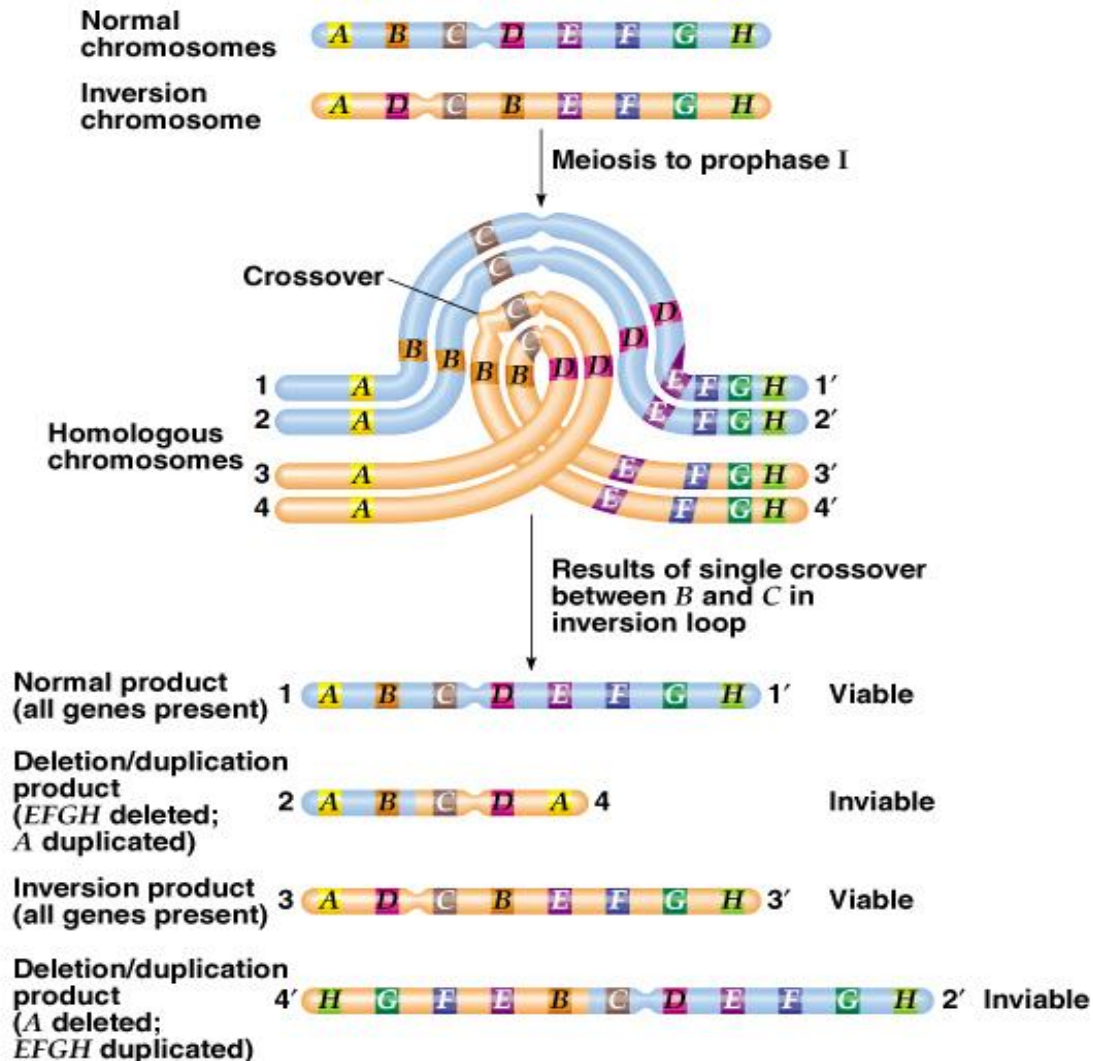
## b) Products of meiotic crossover

Normal chromosome  
Inversion chromosome

Meiosis to prophase I



# crossover within a heterozygous, pericentric inversion loop



# Translocation

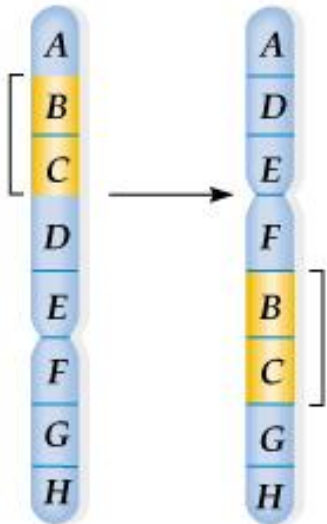
## Animation: Meiosis in a Translocation Heterozygote

1. A change in location of a chromosome segment is a translocation. No DNA is lost or gained. Simple translocations are of two types (Figure 21.12):
  - a. **Intrachromosomal**, with a change of position within the same chromosome.
  - b. **Interchromosomal**, with transfer of the segment to a nonhomologous chromosome.
2. Gamete formation is affected by translocations.
  - a. In homozygotes with the same translocation on both chromosomes, altered gene linkage is seen.
  - b. Gametes produced with chromosomal translocations often have unbalanced duplications and/or deletions and are inviable, or produce disorders like familial Down syndrome.
  - c. Strains homozygous for a reciprocal translocation form normal gametes.

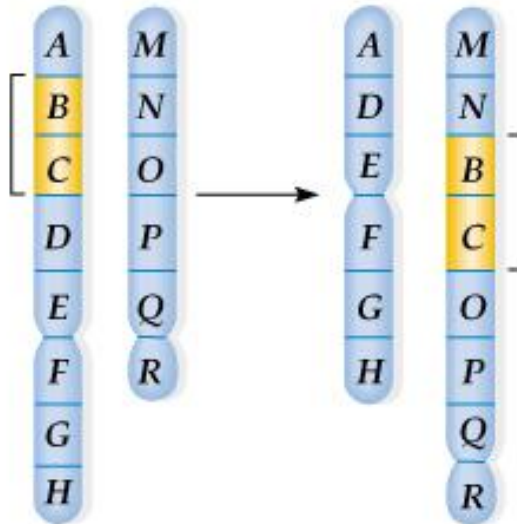


# Translocations

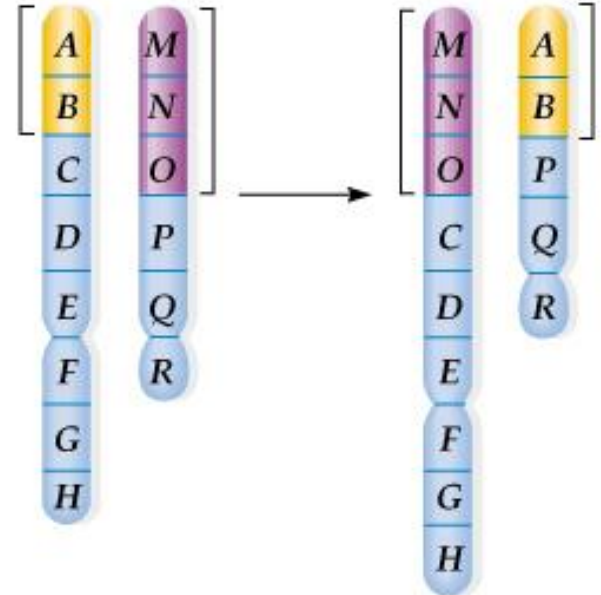
a) Nonreciprocal intrachromosomal translocation



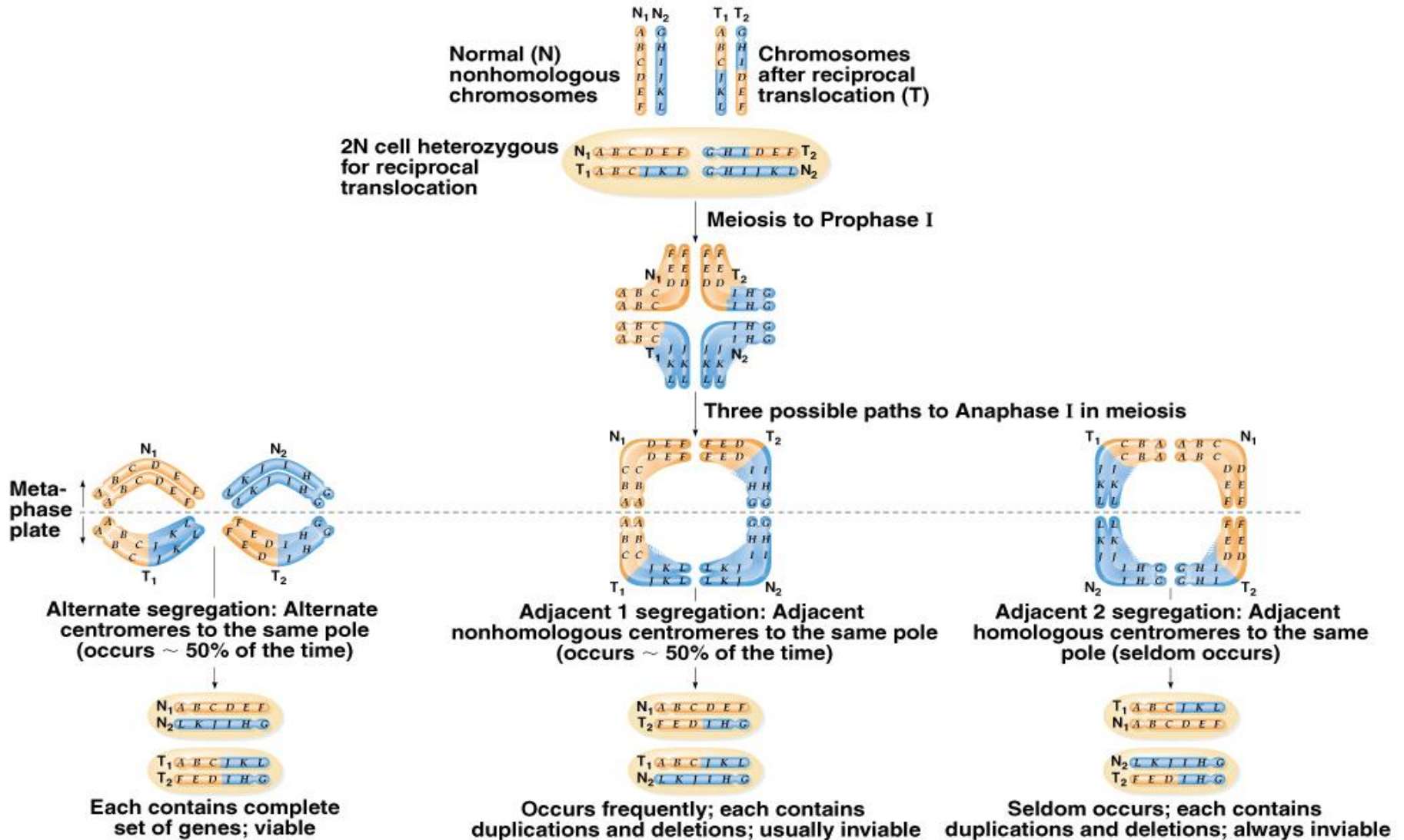
b) Nonreciprocal interchromosomal translocation



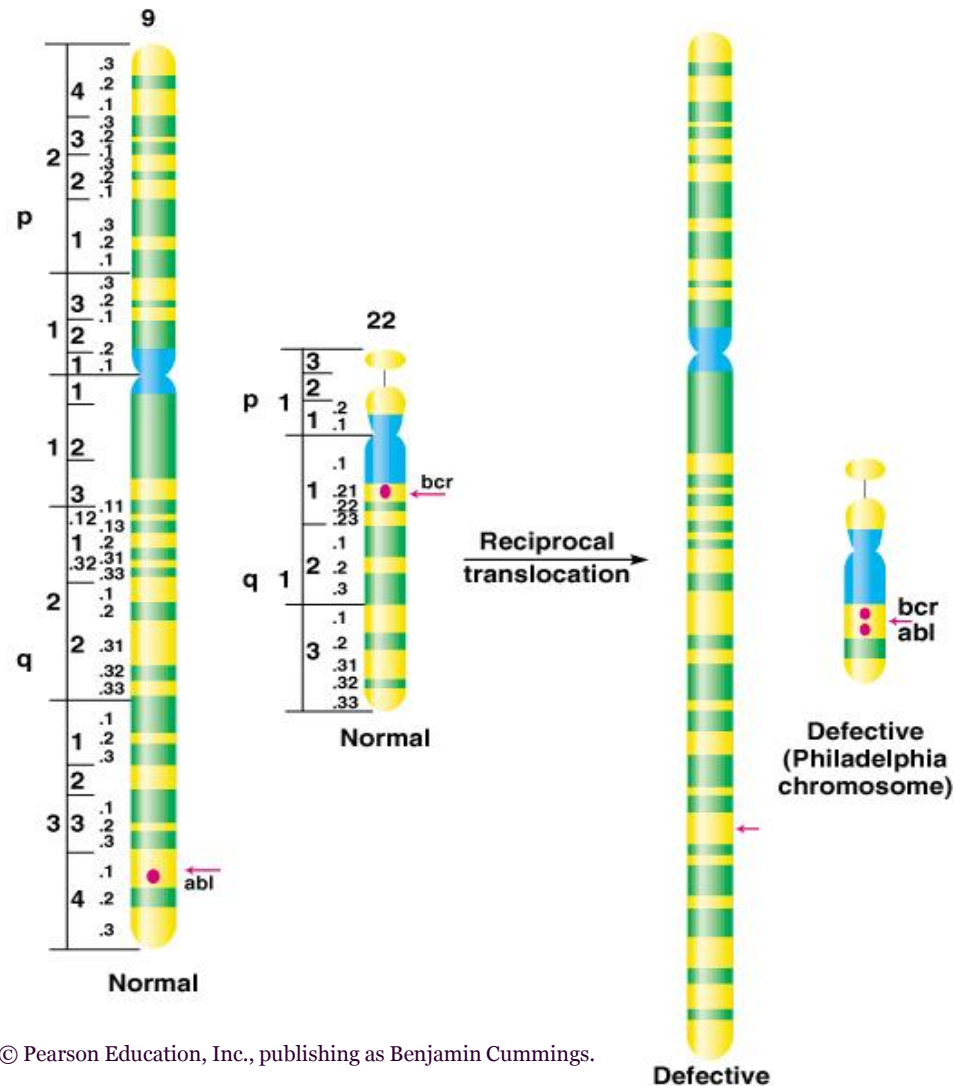
c) Reciprocal interchromosomal translocation



# Meiosis in a translocation heterozygote in which no crossover occurs



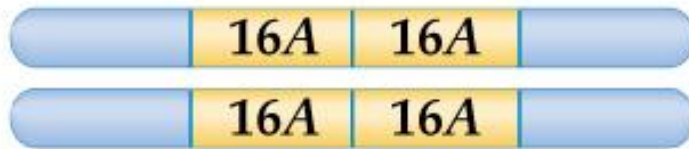
# Origin of the Philadelphia chromosome in chronic myelogenous leukemia (CML) by a reciprocal translocation involving chromosomes 9 and 22



## Position Effect

1. Sometimes inversions or translocations change phenotypic expression of genes by the position effect, for example by moving a gene from euchromatin to heterochromatin (transcription generally occurs in euchromatin but not heterochromatin).
2. An example is the white-eye ( $w$ ) locus in *Drosophila*:
  - a. An inversion moves the  $w$  gene from a euchromatin region of the X chromosome to a position in heterochromatin.
  - b. In a  $w^+$  male, or a  $w^+/w$  female, where  $w^+$  is involved in the inversion, the eyes will have white spots resulting from the cells where the  $w$  allele was moved and inactivated.

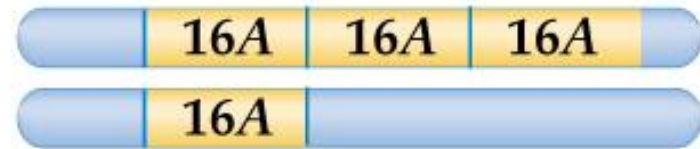
# Position effect and *Bar* eye in *Drosophila*



Homozygous *Bar*♀



Average number  
of facets = 68



Heterozygous  
double-*Bar*/normal♀



Average number  
of facets = 45

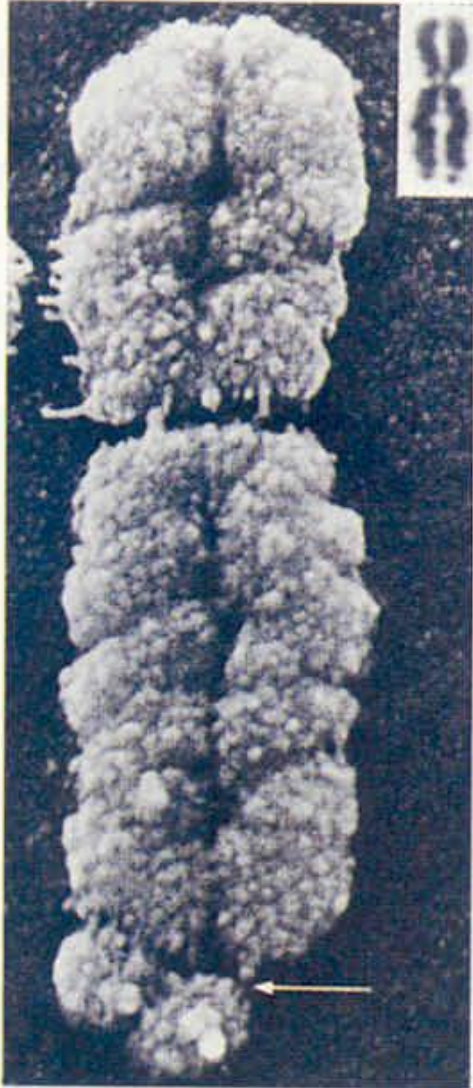
# Fragile Sites and Fragile X Syndrome

1. Chromosomes in cultured human cells develop narrowings or unstained areas (gaps) called fragile sites; over 40 human fragile sites are known.
2. A well-known example is fragile X syndrome, in which a region at position Xq27.3 is prone to breakage and mental retardation may result.
  - a. Fragile X syndrome has an incidence in the U.S. of about 1/1,250 in males, and 1/2,500 in females (heterozygotes).
  - b. Inheritance follows Mendelian patterns, but only 80% of males with a fragile X chromosome are mentally retarded. The 20% with fragile X chromosome but a normal phenotype are called normal transmitting males.
  - c. About 33% of carrier (heterozygous) females

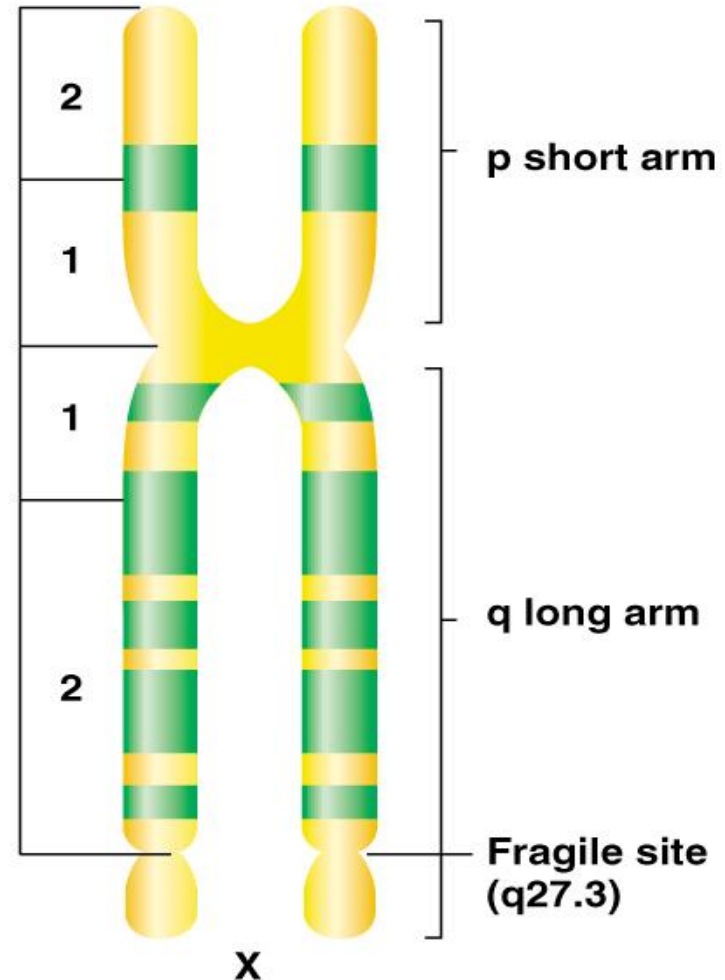


# Diagram of a human X chromosome showing the location of the fragile site responsible for fragile X syndrome

a)



b)



# Variations in Chromosome Number

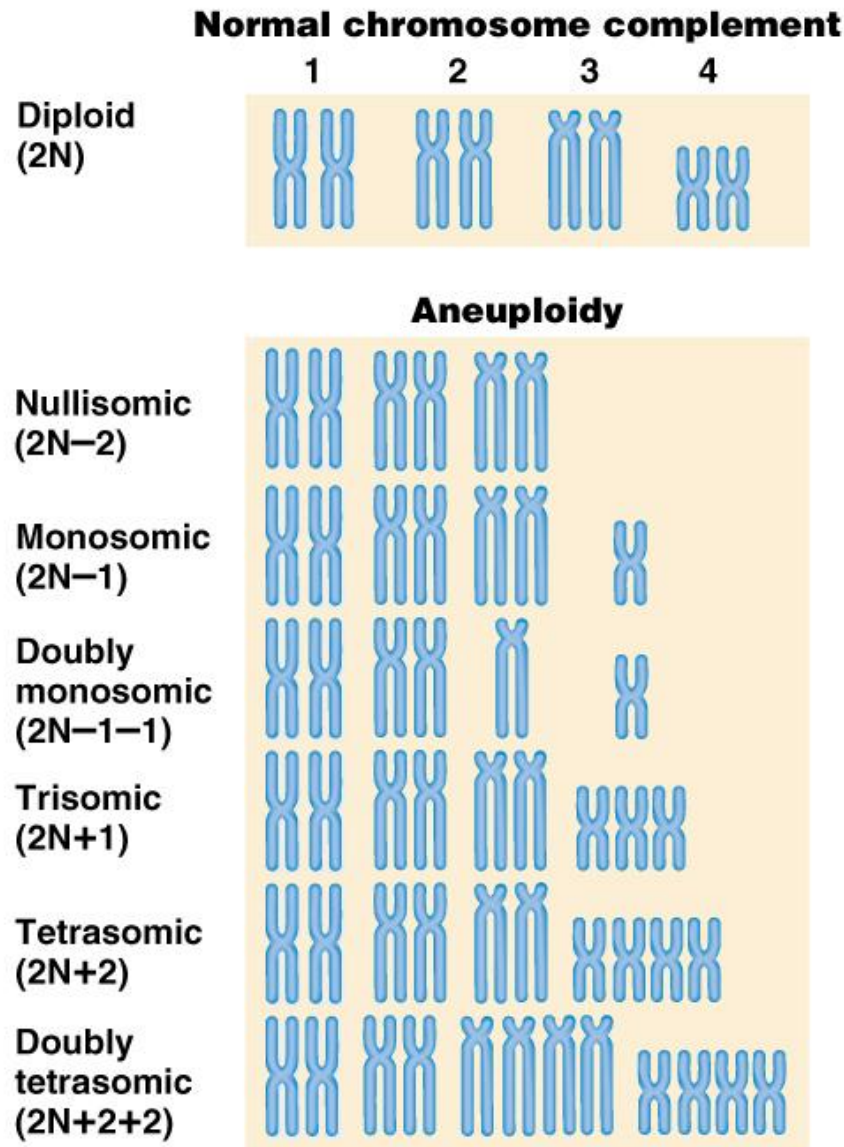
1. An organism or cell is **euploid** when it has one complete set of chromosomes, or exact multiples of complete sets. Eukaryotes that are normally haploid or diploid are euploid, as are organisms with variable numbers of chromosome sets.
2. **Aneuploidy** results from variations in the number of individual chromosomes (not sets), so that the chromosome number is not an exact multiple of the haploid set of chromosomes.



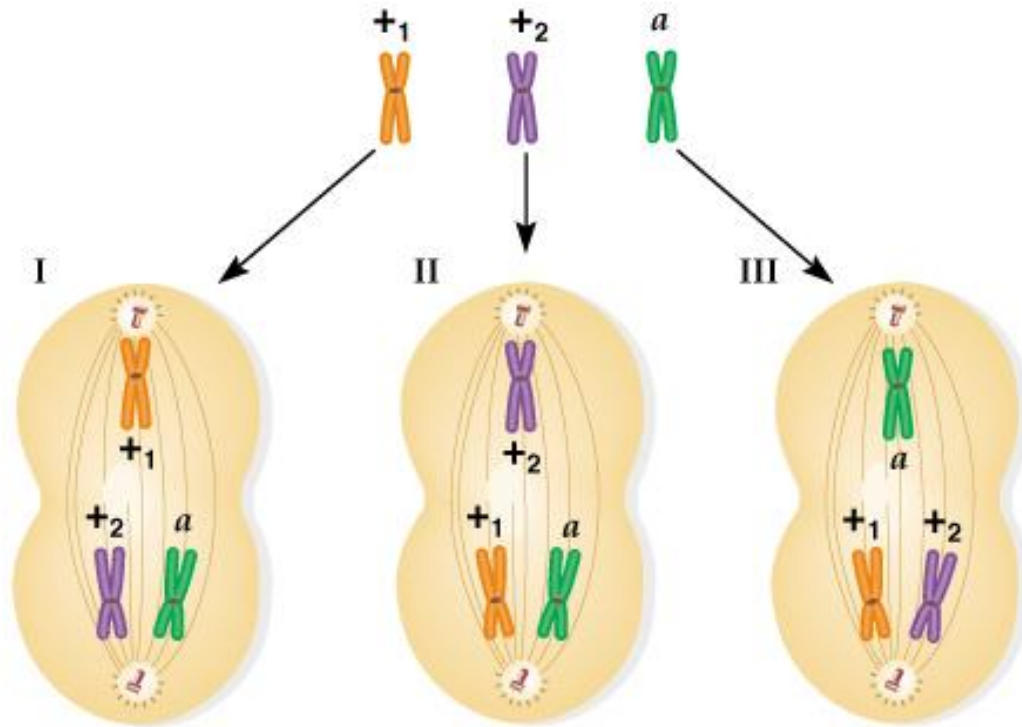
# Changes in One or a Few Chromosomes

1. Aneuploidy can occur due to nondisjunction during meiosis.
2. Autosomal aneuploidy is not well tolerated in animals, and in mammals is detected mainly after spontaneous abortion. Aneuploidy is much better tolerated in plants. There are four main types of aneuploidy (Figure 21.17):
  - a. Nullisomy involves loss of 1 homologous chromosome pair (the cell is  $2N - 2$ ).
  - b. Monosomy involves loss of a single chromosome ( $2N - 1$ ).
  - c. Trisomy involves one extra chromosome, so the cell has three copies of one, and two of all the others ( $2N + 1$ ).
  - d. Tetrasomy involves an extra chromosome pair, so the cell has four copies of one, and two of all the others ( $2N + 2$ ).
3. More than one chromosome or chromosome pair may be lost or added. Examples:
  - a. A double monosomic aneuploidy has two separate chromosomes present in only one copy each ( $2N - 1 - 1$ ).
  - b. A double tetrasomic aneuploidy has two chromosomes present in four copies each ( $2N + 2 + 2$ ).

# Normal (theoretical) set of metaphase chromosomes in a diploid (2N) organism (*top*) and examples of aneuploidy (*bottom*)



# Meiotic segregation possibilities in a trisomic individual



Gametes produced  
after 2nd meiotic division

	haploid	disomic
I	+1	+2/a
II	+2	+1/a
III	a	+1/+2

In sum: 2 +/ a : 2 + : 1 + /+ : 1 a

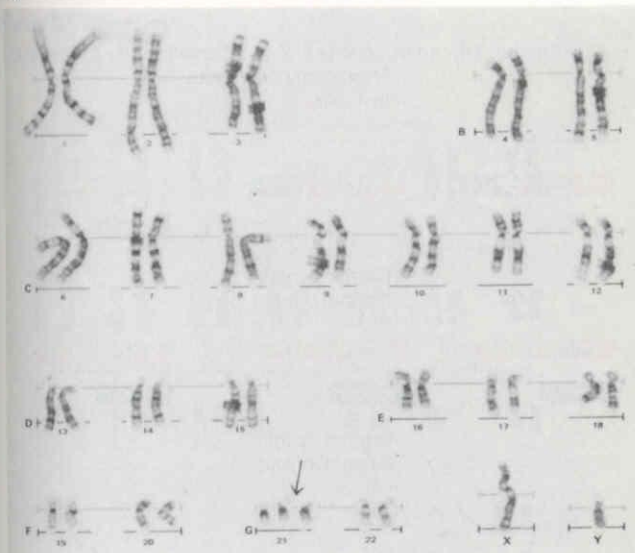
**Table 21.2** Relationship Between Age of Mother and Risk of Trisomy-21

Age of Mother	Risk of Trisomy-21 in Child
16–26	7.7/10,000
27–34	4/10,000
35–39	29/10,000
40–44	100/10,000
45–47	333/10,000
All mothers combined	14.3/10,000

**Figure 21.19**

Trisomy-21 (Down syndrome). (a) Karyotype. (b) Individual.

a)



b)

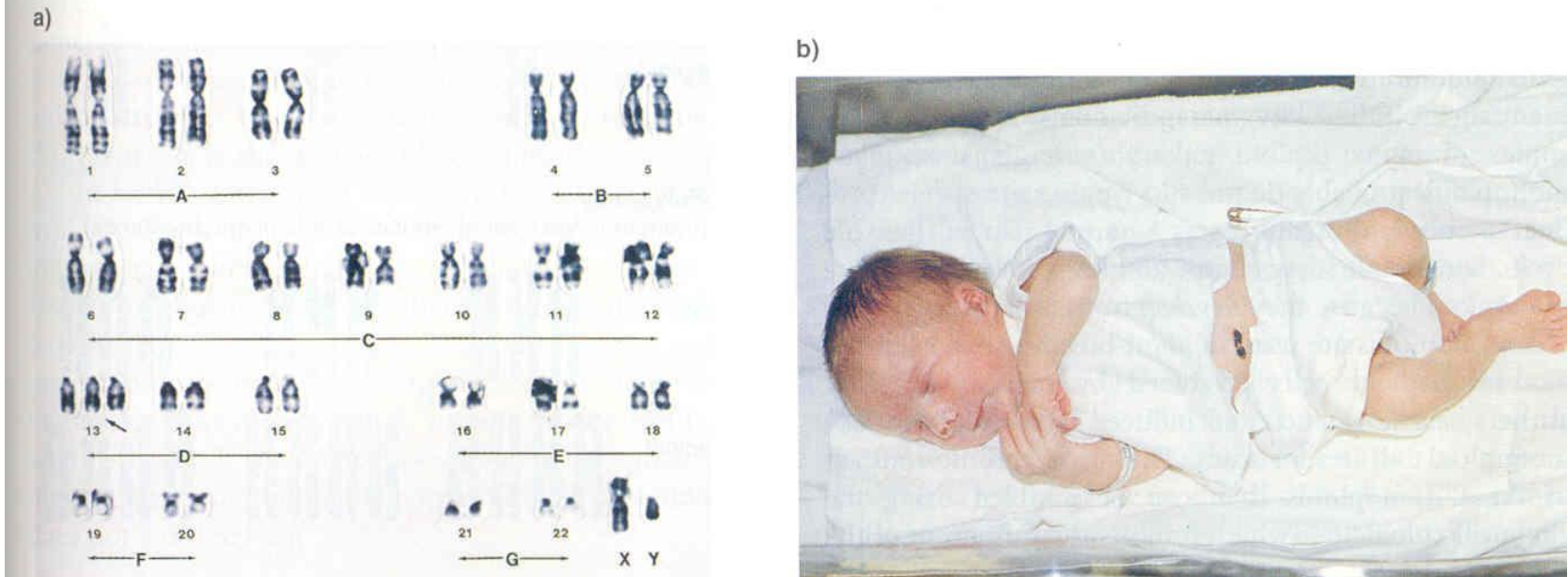


Trisomy-13 (Patau syndrome) occurs in  $2/10^4$  live births, and most die within the first 3 months. Characteristics include (Figure 21.22):

- i. Cleft lip and palate.
- ii. Small eyes.
- iii. Polydactyly (extra fingers and toes).
- iv. Mental and developmental retardation.

Figure 21.22

Trisomy-13 (Patau syndrome). (a) Karyotype. (b) Individual.





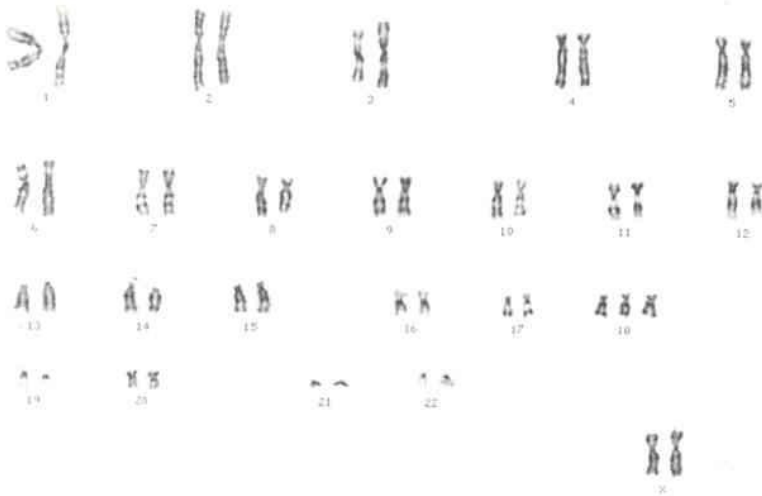
Trisomy-18 (Edwards syndrome) occurs in  $2.5/10^4$  live births, and 90% die within 6 months. About 80% of Edwards syndrome infants are female. Characteristics include (Figure 21.19):

- i. Small size with multiple congenital malformations throughout the body.
- ii. Clenched fists.
- iii. Elongated skull.

**Figure 21.23**

Trisomy-18 (Edwards syndrome). (a) Karyotype. (b) Individual.

a)



b)

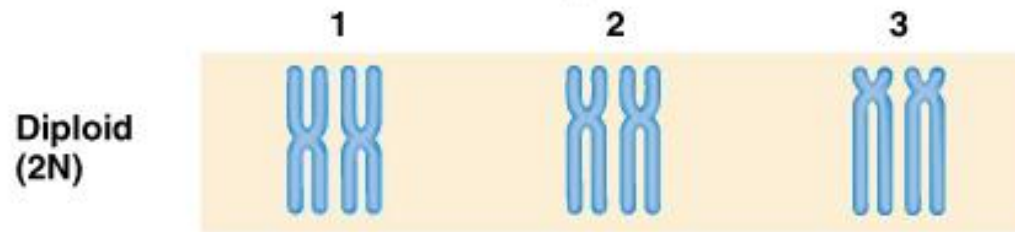


# Changes in Complete Sets of Chromosomes

1. **Monoploidy** and **polyploidy** involve complete sets of chromosomes, and so both are cases of euploidy. Euploidy is lethal in most animal species, but often tolerated in plants, where it has played a role in speciation and diversification.
2. **Monoploidy** and **polyploidy** can result when either round of meiotic division lacks cytokinesis, or when meiotic nondisjunction occurs for all chromosomes.
  - a. Complete nondisjunction at meiosis I will produce  $1/2$  gametes with normal chromosomes,  $1/2$  with no chromosomes.
  - b. A gamete with two sets of chromosomes fused with a normal gamete produces a triploid ( $3N$ ) zygote.
  - c. Fusion of two gametes that each have two sets of chromosomes produces a tetraploid ( $4N$ ) zygote.
  - d. Polyploidy of somatic cells can result from mitotic nondisjunction of complete chromosome sets.

# Variations in number of complete chromosome sets

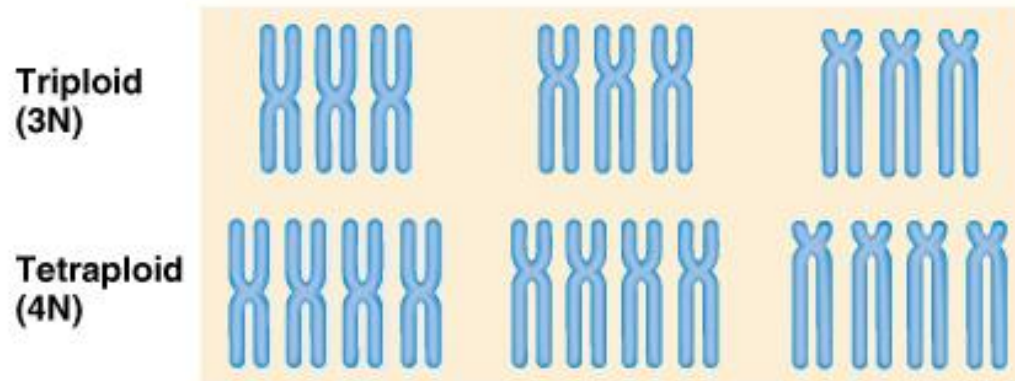
## Normal chromosome complement



### a) Monoploidy (only one set of chromosomes)



### b) Polyploidy (more than the normal number of sets of chromosomes)





3. **Monoploidy** is rare in adults of diploid species due to recessive lethal mutations.

Plant experiments often use monoploids.

- i. Haploid cells are isolated from plant anthers and grown into monoploid cultures.
- ii. **Colchicine** (which inhibits mitotic spindle formation) allows chromosome number to double, producing completely homozygous diploid breeding lines.
- iii. Mutant genes are easily identified in monoploid organisms.

4. Polyploidy involves three or more sets of chromosomes, and may occur naturally (e.g., by breakdown of the mitotic spindle), or by induction (e.g., with chemicals such as colchicine).

Nearly all plants and animals probably have some polyploid tissues. **Examples:**

- i. Plant endosperm is triploid.
- ii. Liver of mammals (and perhaps other vertebrates) is polyploid.
- iii. North American sucker fish, salmon and some salamanders are polyploid.
- iv. Wheat is hexaploid ( $6N$ ) and the strawberry is octaploid ( $8N$ ).

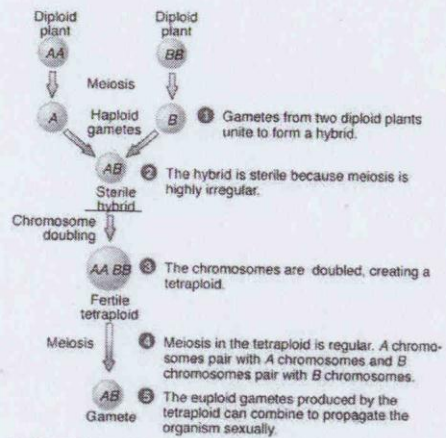
Polyploidy is more common in plants, probably due to self-fertilization, allowing an even-number of polyploids to produce fertile gametes and reproduce.

Plant polyploidy occurs in two types:

- i. **Autopolyploidy** results when all sets of chromosomes are from the same species, usually due to meiotic error. Fusion of a diploid gamete with a haploid one produces a triploid organism. Examples include:
  - (1) "Seedless" fruits like bananas, grapes and watermelons.
  - (2) Grasses, garden flowers, crop plants and forest trees.

ii. **Allopolyploidy** results when the chromosomes are from two different organisms, typically from the fusion of haploid gametes followed by chromosome doubling. For example:

- (1) Fusion of haploid gametes from plant 1 and plant 2 produces an  $N_1 + N_2$  hybrid plant. No chromosomal pairing occurs at meiosis, viable gametes are not produced and the plants are sterile.
- (2) Rarely, division error doubles the chromosome sets ( $2N_1 + 2N_2$ ). The diploid sets function normally in meiosis, and fertile allotetraploid plants result.
- (3) An example is crosses between cabbages (*Brassica oleracea*) and radishes (*Raphanus sativus*), which both have a chromosome number of 18.



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(a) The F1 hybrids have 9 chromosomes from each parent, and have a morphology intermediate between cabbages and radishes. They are mostly sterile.

(b) A few seeds, some fertile, can be produced by the F1 through meiotic errors.

(c) Somatic cells in the resulting plants have 36 chromosomes, a full diploid set from both cabbages and radishes.

(d) These fully fertile plants look much like the F1 hybrids, and are named *Raphanobrassica*.

\*\*\*\*\* Polyploidy is the rule in agriculture, where polyploids include all commercial grains (e.g., bread wheat, *Triticum aestivum*, an allohexaploid of three plant species), most crops and common flowers.

# Mutation Nomenclature

- A nucleotide change is denoted first by the nucleotide number of that base, the original nucleotide, a greater than symbol (>) and the new nucleotide at that position. In genomic DNA, the nucleotide symbols are capitalized; in mRNA, they are lowercase.



- If the full genomic sequence is not known, the nucleotides in an intron (referred to by the expression "intervening sequence," or IVS) are counted as +1, +2, and so on, in which +1 is the invariant G of the GT in the 5' splice donor site, or as -1, -2, and so on, counting back from the highly invariant G of the AG 3' splice acceptor site. Small deletions are indicated by the numbers of the nucleotides deleted, separated by underscore (\_\_\_\_), followed by the term *del*, and then the actual nucleotides that have been deleted.

- Small insertions are designated by *ins* after the two nucleotides between which the insertion occurred, followed by the actual nucleotides inserted.
- A missense or nonsense mutation can be described at the level of the protein by giving the correct amino acid, the position of that residue, and the amino acid that replaced the normal one.
- In cDNA, the A of the translational start ATG is designated +1. The next base upstream is -1; there is no 0. The amino-terminal methionine is numbered +1 in the protein

# Examples

- c.1444g>a: a mutation at position 1444 in the hexosaminidase A cDNA causing Tay-Sachs disease
- g.IVS33+2T>A: a mutation substituting an A for T in a splice donor site GT of intron 33 of a gene
- g.IVS33-2A>T: a mutation substituting a T for an A in the highly conserved AG splice acceptor site in the same intron
- c.1524\_1527delCGTA: a deletion of four nucleotides, numbers 1524 through 1527 in cDNA

- c.1277\_1278insTATC: a four-base insertion between nucleotides 1277 and 1278 in the hexosaminidase A cDNA, a common mutation causing Tay-Sachs disease
- Glu6Val: a missense mutation, glutamic acid to valine at residue 6 in  $\beta$ -globin, that causes sickle cell disease
- Gln39X: a nonsense mutation, glutamine to stop codon (X) at position 39 in  $\beta$ -globin, that causes  $\beta^0$ -thalassemia.